02-4070. If a Petition for extension of time is needed, this paper is to be considered such Petition.

The specification has been amended to update reference to patent applications. Accordingly, no new matter has been added.

Claims 11-17, 22-35 and 154-191 are presently pending. Claims 18-21 and 36-153, which are directed to non-elected subject matter that has been withdrawn from consideration, have been cancelled without prejudice or disclaimer. Applicant reserves the right to pursue the subject matter of cancelled claims 18-21 and 36-153 in continuation applications that claim the benefit of the filing date of the subject application.

Claims 1-7, 9-15, and 22-32 have been amended herein to obviate rejections under 35 U.S.C. § 112, second paragraph and/or amended to correct obvious clarity or typographical errors. The amendments finds basis in the specification and claims as originally filed. For example, "conditions in which high cell densities can be achieved exceeding 1 x 10^6 cells/ml" finds basis at page 13, lines 25-26, page 34, lines 6-7, and original claim 150; "cell activation and cell proliferation" finds basis at page 13, lines 1-4, page 17, lines 3-6 and page 33, lines 6-7.

The amendments to the claims also are designed to more particularly point out and distinctly claim the subject matter that applicant regards as the invention by clarifying certain language and addressing issues raised in the Office Action. Therefore, since the amendments change the form, not the substance of the claimed subject matter, no new matter has been added, nor have the claims been amended to avoid any art of record.

New claims 154-191, which find basis in the specification and claims as originally filed, have been added. Thus, no new matter has been added.

INVENTOR'S DECLARATION

The Examiner alleges the inventor's Declaration is defective because it does not recite the Serial Number of the provisional application and the application number of the PCT to which priority has been claimed. The Declaration, however, was correct at the time it was filed because neither the provisional application number nor the PCT application Serial Number were available at the time of execution. It is respectfully submitted that there is no requirement that a Declaration must be updated during prosecution of the application. In the interest of advancing prosecution of the application, a newly executed Declaration by the inventor will be filed under separate cover.

REJECTION OF CLAIMS 1-17 AND 22-35 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-17 and 22-35 are rejected under 35 U.S.C. § 112, first paragraph, because the full scope of the claimed subject matter is allegedly not enabled by the specification because it is alleged that the specification does not provide any specific examples where greater than 1×10^{10} cells are generated, or where 1×10^{10} cells are produced by treatment with other than anti-CD3, anti-CD28 or anti-CD5 antibody, and that the claims and the specification teach that the method is for producing greater than 1×10^{10} cells, but no actual examples of this capability are provided. It is further alleged that the specification does not provide any evidence to support that clinically relevant number of T cells can be generated by treatment with a single monoclonal antibody. The Examiner cites to June et al. (WO 95/33823, page 5) as evidence that at least two signals are required to achieve T cell stimulation/growth.

Reconsideration and withdrawal of the rejection is respectfully requested in view of the amendments to the claims and the following remarks.

Relevant Law

It is incumbent upon the examiner to first establish a prima facie case of non-enablement. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369-70 (CCPA 1971).

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. . . it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.)

Id. (emphasis in original); See also Fiers v. Revel, 984 F.2d 1164, 1171-72, 25 USPQ2d 1601, 1607 (Fed. Cir. 1993);, Gould v. Mossinghoff, 229 USPQ 1, 13 (D.D.C. 1985), aff'd in part, vacated in part, and remanded sub nom. Gould v. Quigg, 822 F.2d 1074, 3 USPQ2d 1302 ("there is no requirement in 35 U.S.C. § 112 or anywhere else in patent law that a specification convince persons skilled in the art that the assertions in the specification are correct").

In order to satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original.

Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." In re Marzocchi et al., 469 USPQ 367 (CCPA 1971)(emphasis added).

The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims (i.e. the "Forman factors"). Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Failure to State a prima facie Rejection for Lack of Enablement

Preparation of clinically relevant numbers of cells

The Examiner has failed to state a prima facie rejection for lack of enablement with respect to the issue of expanding T cells to clinically relevant numbers of greater than 1 x 10^{10} cells. First, this alleged lack of enablement is not supported by any reasons. The basis for the rejection appears to rest solely on the alleged lack of any specific examples in the specification that demonstrate production of greater than 1 x 10^{10} cells (see Office Action, page 3, eight lines from the bottom).

This basis for the rejection is incorrect. First, there is no requirement that specification exemplify every embodiment. Second, Examples 2 and 3 of the specification provide actual evidence that clinically relevant numbers of T cells exceeding 1 x 10^{10} not only can be produced by the claimed method, but have been produced. For example, the Table on page 55 of the specification discloses production of clinically relevant numbers of CD4+ Th1, CD4+ Th2,

and CD8+ cells after 54 days in culture. In addition, page 56 demonstrates production of greater than 1 x 10^{10} CD4+ cells using a different antibody combination from that used for the data set forth in the Table on page 55. Thus, the specification provides ample actual evidence that the claimed methods produce clinically relevant numbers of T cells of various types and under various conditions in excess of 1 x 10^{10} cells.

A prima facie rejection for lack of enablement with respect to the issue of expanding clinically relevant numbers of T cells using activating proteins other than anti-CD3 + anti-CD28 or anti-CD3 + anti-CD28 and anti-CD5 monoclonal antibodies has not been set forth. Again, this allegation is without support and appears to rest solely on the absence of any specific examples in the specification where cells are expanded to greater than 1 x 10^{10} cells using activating proteins other than anti-CD3 + anti-CD28 or anti-CD3 + anti-CD28 and anti-CD5 monoclonal antibodies. There is no requirement in patent law that the scope of the claims must be limited to the preferred embodiments that are supported by direct evidence:

> it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it. In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960).
>
> Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee is not only entitled to narrow claims, particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Futhermore, the specification describes and exemplifies in detail a method for identifying and selecting activating proteins. For example, at page 17, line 29, the specification states:

> Suitable mitogenic antibodies may be identified empirically by testing selected antibodies singly or in combination for the ability to increase numbers of a specific effector cell. Suitable mitogenic antibodies or combinations thereof will increase the number of cells in a selected time period, typically 1 to 10 days, by at least about 50%, preferably about 100% and more preferably 150-200% or more, compared to the numbers of cells in the absence of the antibody.

The specification exemplifies use of CD4, CD8, CD11a, CD27, CD28, CD44 and CD45RO for expansion, and exemplifies testing of combinations of antibodies (page 50) for use in the method. Thus, the specification teaches a relatively simple empirical method for identifying activating and proliferation signals.

The specification also teaches numerous combinations of signals that can be used (see, e.g., page 32):

> To provide the first signal, it is preferable to activate cells with mAb to the CD3/TCR complex, but other suitable signals, such as, but not limited to, antigens, super antigens, polyclonal activators, anti-CD2 and anti-TCR antibodies, may be used. Other suitable agents can be empirically identified. Immobilized or cross-linked anti-CD3 mAb, such as OKT3 or 64.1, can activate T-cells in a polyclonal manner [see, Tax, et al. (1983) Nature 304:445]. Other polyclonal activators, however, such as phorbol myristate acetate can also be used [see, e.g., Hansen, et al. (1980) Immunogenetics 10:247].
>
> Monovalent anti-CD3 mAb in the soluble phase can also be used to activate T-cells [see, Tamura, et al. (1992) J. Immunol. 148:2370]. Stimulation of CD4+ cells with monovalent anti-CD3 mAb in the soluble form is preferable for expansion of Th2 cells, but not Th1 cells [see, deJong, et al. (1992) J. Immunol. 149:2795]. Soluble heteroconjugates of anti-CD3 and anti-T-cell surface antigen mAb can preferentially activate a particular T-cell subset [see, Ledbetter, et al. (1988) Eur. S. Immunol. 18:525]. Anti-CD2 mAb can also activate T-cells [see, Huet, et al. (1986) J. Immunol. 137:1420]. Anti-MHC class II mAb can have a synergistic effect with anti-CD3 in inducing T-cell proliferation [see, Spertini, et al. (1992) J. Immunol. 149:65]. Anti-CD44 mAb can activate T-cells in a fashion similar to anti-CD3 mAb. See, Galandrini, et al. (1993) J. Immunol. 150:4225] . . .

To then cause proliferation of such activated T cells, a second signal is required. A variety of mAb singly or in combination can provide the second signal for T-cell proliferation. Anti-IL-4R mAb (specific for the interleukin-4 receptor molecule) can enhance the proliferation of the Th2 cells [see, Lindquist, et al. (1993) J. Immunol. 150:394]. Immobilized ligands or mAb against CD4, CD8, CD11a (LFA-1), CD49 (VLA), CD45RO, CD44 and CD28 can also be used to enhance T-cell proliferation [see, Manger, et al. (1985) J. Immunol. 135:3669; Hara, et al. (1985) J. Exp. Med. 161:1513; Shimizu, et al. (1990) J. Immunol. 145:59; and Springer, (1990) Nature 346:425]. Cell surface proteins that are ligans to B-cells are preferred targets for Th2 cell proliferation, while macrophage ligands are preferred for Th1 cell proliferation.

Anti-CD28 mAb in combination with anti-CD3 or anti-CD2 induces a long lasting T-cell proliferative response [see, Pierres, et al. (1988) Eur. J. Immunol. 18:685]. Anti-CD28 mAb in combination with anti-CD5 mAb results in an enhanced proliferative response that can be sustained for weeks [see, Ledbetter, et al. (1985) J. Immunol. 135:2331]. Anti-CD5 mAb alone can also provide a second signal for T-cell proliferation [see, Vandenberghe et al. (1991) Eur. J. Immunol. 21:251]. Other mAb known to support T-cell proliferation include anti-CD45 and CD27 [see, Ledbetter, et al. (1985) J. Immunol. 135:1819 and Van Lier, et al. (1987) J. Immunol. 139:1589].

To determine the combination of mAbs or proteins that optimally induce sustained regulatory cell proliferation, a screening procedure using combinations of these mAbs or proteins is used. The cells are incubated with various combinations of these substances and screened for growth by analysis of ^{3}H-thymidine incorporation or equivalent methods. The group demonstrating the best growth characteristics is selected for use in the medium.

The specification, thus, touche a variety of signals for activation and inducing proliferation of cells.

Furthermore, the claims recite that clinically relevant numbers must be produced. Claim 1 specifies the density of the resulting cells. The claims only encompass antibodies that will yield the requisite result.

Thus, instant claims are functionally limited to operative embodiments. Only signals that meets the readily determinable criteria the ability to induce activation and proliferation to a clinically relevant number of cells are encompassed within the scope of the claims. This is similar to the situation in Ex parte Mark, 12 USPQ2d 1904 (Bd. App.) in which the Board concluded claims that were functionally limited to operative embodiments are enabled.

In Ex parte Mark, 12 USPQ2d 1904 (Bd. App.), claims for cys-depleted muteins of biologically active proteins that require mutein to retain biological activity of the native protein were deemed enabled since one of skill in art would be able to routinely determine whether deletion or replacement of cys residue would result in a mutein which is within scope of claims. The fact that a given protein may not be amenable for use as claimed was held not to mitigate against conclusion of enablement. Similarly, whether combinations of antibodies or other signals may not, when used in the claimed method, produce clinically relevant numbers or may be outside the claims should not mitigate enablement of the instant claims, which clearly specify the criteria for the selected antibodies or other signals for use in the methods as claimed.

As noted above, the inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

It would not require undu experim ntation to us the claimed methods

The claims are commensurate in scope with the disclosure, which exemplifies particular embodiments within the scope of the claims and also teaches how one of skill in the art can obtain other embodiments within the scope of the claims. In particular, there is an enormous amount of guidance presented in the specification, the level of skill in the art is high, there are several working examples and the experiments have been repeated. Therefore, it would not require undue experimentation for one of skill in the art to make and use the claimed subject matter.

Evaluation of the above Factors

1. The scope of the claims

Claim 1 is directed to a method for generating clinically relevant numbers of T lymphoid cells by contacting mononuclear cells in the absence of IL-2 with one or more activating proteins and then expanding the cells to high cell density (at least about 1×10^9 cells/Liter).

Claim 22 is directed to a method for generating clinically relevant numbers of regulatory T lymphoid cells by activating mononuclear cells to alter their cytokine production profile and inducing cell proliferation under conditions that produce high cell density.

2. Level of skill

The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application, authored and reviewed by those known in the art, further evidences the high degree of skill in this art.

3. The amount of direction and guidance presented, and teachings in specification

All of the claims are directed to a method for producing clinically relevant numbers of cells. The specification at page 20, line 1, defines a clinically relevant number of cells as:

> a composition that contains at least 10^9, preferably greater than 10^9, more preferably at least 10^{10} cells, and most preferably more than 10^{10} cells, in which the majority of the cells have a defined regulatory or effector function . . . .

Elsewhere, the specification states that when used for treating a particular disease, a clinically relevant number is the amount sufficient to alter immune balance. This amount is typically at least about 10^9, but may be less.

All of the claims require that the cells are activated and induced to proliferate with two or more activating proteins specific for cell surface proteins present on the cells in an amount sufficient to induce *ex vivo* cell activation and cell proliferation. The specification at page 17, beginning at line 3, defines an activating protein as activating proteins as:

> molecules that when contacted with a T-cell population cause the cells to proliferate. T-cells generally require two signals to proliferate. Activating proteins thus encompasses the combination of proteins that provide the requisite signals, which include an initial priming signal and a second co-stimulatory signal.

The specification at page 17 teaches that the first signal requires a single agent, and provides several examples, including anti-CD3 mAb, anti-CD2 mAb, anti-TCR mAb, PHA, and PMA and other such signals. Furthermore, the specification beginning at page 32, line 12 provides citations to a variety of activating agents for a first signal is provided as follows:

> Other suitable agents can be empirically identified. Immobilized or cross-linked anti-CD3 mAb, such as OKT3 or 64.1, can activate T-cells in a polyclonal manner [see, Tax, et al. (1983) Nature 304:445]. Other polyclonal activators, however, such as phorbol myristate acetate can also be used [see, e.g., Hansen, et al. (1980) Immunogenetics 10:247].
>
> Monovalent anti-CD3 mAb in the soluble phase can also be used to activate T-cells [see, Tamura, et al. (1992) J. Immunol. 148:2370]. Stimulation of CD4+ cells with monovalent anti-CD3 mAb in the soluble form is preferable for expansion of Th2 cells, but not Th1 cells [see, deJong, et al. (1992) J. Immunol. 149:2795]. Soluble heteroconjugates of anti-CD3 and anti-T-cell surface antigen mAb can preferentially activate a particular T-cell subset [see, Ledbetter, et al. (1988) Eur. S. Immunol. 18:525]. Anti-CD2 mAb can also activate T-cells [see, Huet, et

> al. (1986) J. Immunol. 137:1420]. Anti-MHC class II mAb can have a synergistic effect with anti-CD3 in inducing T-cell proliferation [see, Spertini, et al. (1992) J. Immunol. 149:65]. Anti-CD44 mAb can activate T-cells in a fashion similar to anti-CD3 mAb. See, Galandrini, et al. (1993) J. Immunol. 150:4225].

The specification at page 17 also teaches the requirement of a second signal for T cell expansion that involve one or more agents, and provides examples such anti-CD28, anti-CD40L, cytokines and other such signals. Again, the specification beginning at page 33, line 7 recites a variety of activating agents as second signals as follows:

> A variety of mAb singly or in combination can provide the second signal for T-cell proliferation. Anti-IL-4R mAb (specific for the interleukin-4 receptor molecule) can enhance the proliferation of the Th2 cells [see, Lindquist, et al. (1993) J. Immunol. 150:394]. Immobilized ligands or mAb against CD4, CD8, CD11a (LFA-1), CD49 (VLA), CD45RO, CD44 and CD28 can also be used to enhance T-cell proliferation [see, Manger, et al. (1985) J. Immunol. 135:3669; Hara, et al. (1985) J. Exp. Med. 161:1513; Shimizu, et al. (1990) J. Immunol. 145:59; and Springer, (1990) Nature 346:425]. Cell surface proteins that are ligans to B-cells are preferred targets for Th2 cell proliferation, while macrophage ligands are preferred for Th1 cell proliferation.
>
> Anti-CD28 mAb in combination with anti-CD3 or anti-CD2 induces a long lasting T-cell proliferative response [see, Pierres, et al. (1988) Eur. J. Immunol. 18:685]. Anti-CD28 mAb in combination with anti-CD5 mAb results in an enhanced proliferative response that can be sustained for weeks [see, Ledbetter, et al. (1985) J. Immunol. 135:2331]. Anti-CD5 mAb alone can also provide a second signal for T-cell proliferation [see, Vandenberghe et al. (1991) Eur. J. Immunol. 21:251]. Other mAb known to support T-cell proliferation include anti-CD45 and CD27 [see, Ledbetter, et al. (1985) J. Immunol. 135:1819 and Van Lier, et al. (1987) J. Immunol. 139:1589].

The specification further teaches use of a screening procedure to select combinations of protein activating agents to properly sustain regulatory cell proliferation to clinically relevant cell numbers. For example, page 33, line 28 to page 34, line 4, and page 48, line 21 to page 51, line 20, describe a screening assay for identifying useful antibody combinations with various types of T cells. It is noted therein that CD4+ and CD8+ cells were well stimulated using

combinations of anti-CD3 + anti-CD5, anti-CD3 + anti-CD28, and anti-CD3 + anti-CD5 + anti-CD28. The specification further teaches at page 18, lines 1-5 the criteria to identify a suitable combinations of activating proteins as that which will:

> increase the number of cells in a selected time period, typically 1 to 10 days, by at least about 50%, preferably about 100% and more preferably 150-200% or more, compared to the numbers of cells in the absence of the antibody.

The specification also provides extensive teachings on how to use selected activating proteins to expand T cells to clinically relevant numbers by growth under conditions that produce high cell density. For example, the specification teaches at page 34, line 8, that cells can be grown in various devices including "stirred tank fermentors, airlift fermentors, roller bottles, culture bags, and other bioreactor devices." The specification further provides at page 34, beginning at line 6, the use of hollow fiber bioreactors to expand cells to clinically relevant cell numbers. Such methods permit cells to be cultured to the required high densities in a minimal volume and reduces the amount of monoclonal antibodies, serum and medium required in the production process. In addition, selection of fibers with molecular weight cut-offs of 6000 daltons will allow continuous feeding and waste product removal while retaining cell derived cytokines in the culture space. A variety of hollow fibre culture systems are disclosed in the specification at page 34, line 28 to page 36, line 5. The preferred hollow fiber system of U.S. Patent No. 5,627,070 is disclosed in the specification at page 36, line 10 to page 37, line 23.

Thus, based on the teachings in the specification one of skill in the art could have selected a combination of activating proteins suitable for inducing cell activation and expansion and could have used the proteins under appropriate conditions of culture to expand the cells to clinically relevant cell numbers.

4. Pr sence of working examples and pr dictability

In addition to the thorough teaching of how select activating proteins and use such proteins to expand T cells to clinically relevant cell numbers, the specification provides **several working examples**, including clinical data, illustrated in exhaustive detail exactly how to use the methods taught by the specification. Specifically, the examples provide details of screening for combinations of activating proteins, collecting mononuclear cells, purifying precursor cell populations, *ex vivo* differentiation of cells, and expansion of cells to clinically relevant cell numbers.

A variety of antibody and interleukin combinations, which included anti-CD3, anti-CD5, anti-CD28, IL-2, and anti-CD45RO, were demonstrated to result in significant stimulation. Furthermore, the specification provides experimental evidence that the screening methods were effective at producing clinically relevant numbers of T lymphoid cells (CD4+ Th1 or Th2, and CD8+) and under conditions that produce high cell density (see e.g., the table at page 55) using activation with anti-CD3 + anti-CD28 + anti-CD5 or with anti-CD3 + anti-CD28.

Conclusion

Therefore, in light of the extensive teachings and examples in the application, the high level of skill in the art and the breadth of the claims, it would not require undue experimentation to make and use the claimed methods.

Response to Specific Issues Raised

The Examiner states that the specification does not disclose any specific examples of where greater than 1×10^{10} cells are actually produced. This is incorrect. The table on page 55 provides an example where both CD4+ and CD8+ cells were produced by day 54 in numbers that exceed 1×10^{10} cells, while page 56, line 26 shows production of greater than 1×10^{10} CD4+ cells by day 72 of culture.

The Examiner also states that the specification does not disclose any specific examples of where greater than 1 x 10^9 or 1 x 10^{10} cells were produced using methods other than anti-CD3 + anti-CD28 or anti-CD3 + anti-CD28 + anti-CD5. As discussed above, the specification teaches a method to test cells against various combinations of activating agents and provides criteria to choose those combinations suited to grow clinically relevant numbers of cells. Also as discussed above, the specification provides numerous examples of the screening method showing useful activating agents other than anti-CD3 + anti-CD28 or anti-CD3 + anti-CD28 + anti-CD5. It is respectfully submitted that in view of the specification and the teachings of the art as a whole, it would not require undue experimentation to identify a variety of activating agents suitable for the claimed methods.

Entitlement to broader claim than only the disclosed sequences

It is unfair and unduly limiting to require an applicant to limit the claims to only the specifically exemplified embodiments. To do so is contrary to the public policy upon which the U.S. patent laws are based. If Applicant is required to limit the claims to only the exemplified embodiments, then those of skill in the art could, by virtue of the teachings of this application, achieve clinically relevant numbers of T cells using different activating proteins than those actually used in the application, but avoid infringing such limited claims. To permit that is simply not fair. The instant application teaches a large variety of activating proteins and a method to select those combinations that are suitable for sustaining growth at high cell density. By providing this disclosure, others will be given the ability to successfully utilize combinations of activating proteins taught in the specification or readily identified using the teachings of the specification and produce clinically relevant numbers of T cells under conditions that produce high cell density. Applicant, therefore, is entitled to a broader scope of coverage than only the embodiments for which evidence is specifically disclosed in the specification.

REJECTION OF CLAIMS 1-7, 11, 13-17, 22-25, 31, and 33-35 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-7, 11, 13-17, 22-25, 31, and 33-35 are rejected under 35 U.S.C. § 112, first paragraph because expansion of "immune cells" or "regulatory immune cells" per se is allegedly not enabled. The Examiner states that the specification enables expansion of T cells and T cell subsets but does not enable expansion of non-T cells, such as macrophages and dendritic cells, which are encompassed within the terms "immune cells" or "regulatory immune cells."

Reconsideration and withdrawal of the rejection is respectfully requested in view of the amendment of the claims to recite "T lymphoid cells."

It is respectfully submitted that the claims have been amended to recite T lymphoid cells in the interest in advancing prosecution, such amendment is not provided to avoid prior art or to limit the scope of coverage of the claims. The specification clearly defines the term immune cells and regulatory immune cells. At page 19, the specification recites:

> a regulatory immune cell is any mononuclear cell with a defined cytokine production profile and in which such cytokine profile does not directly mediate an effector function. A regulatory immune cell is a mononuclear cell that has the ability to control or direct an immune response, but does not act as an effector cell in the response.

The specification also states that the term mononuclear cell is used interchangeably with T lymphoid cell.

Thus it is clear that regulatory immune cells are T lymphoid cells that have a defined cytokine profile and the ability to direct an immune response, but do not participate directly in the response. In contrast, an effector cell is one that participates directly in mediating the immune response.

REJECTION OF CLAIMS 1, 2, 17, 22, 23, 27 and 30 UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1, 2, 17, and 22-35 are rejected as being indefinite under 35 U.S.C. § 112, second paragraph. Various bases for this rejection are set forth and each is discussed in turn. Reconsideration of the grounds for rejection is respectfully requested in view of the amendments of the claims and the following remarks.

1. Claims 2, 17 and 22 are allegedly indefinite because of the recitation of "regulatory immune cells." The specification at page 19 allegedly defines a regulatory cell has having the "ability to control and direct an immune response, but does not act as an effector cell in the response." The Examiner states that this definition is unclear as to what it means or encompasses. It is further stated that Liblau et al. (page 34-38) teaches that Th1 and Th2 are "effector cells" with respect to the pathogenesis of a variety of autoimmune diseases. The Examiner further alleges that Liblau et al. teaches that the lymphokines secreted from Th1 and Th2 cells are involved in the pathogenesis of IDDM. It is concluded that according to the definitions in the specification, Th1, Th2 or Th3 cells would not be classified as regulatory cells because they "function as effector cells and the variety of cytokines they produce also function in a variety of different effector mechanisms."

The rejection is respectfully traversed.

Relevant Law

When "one skilled in the art would understand all of the language in the claims when read in light of the specification," a claim is not indefinite. Rosemount Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), Caterpillar Tractor Co. v. Berco, S.P.A., 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). The claims are definite if they "make clear what subject matter they encompass and thus what the patent precludes others from doing". In re Spiller, 182 USPQ 614 (CCPA 1974). The requirements of § 112, second paragraph are met when one can

"examine the claims to see whether the invention's metes and bounds can be adequately determined from the claim languages". In re Goffe, 188 USPQ 131 (CCPA 1975).

Analysis

First, it is noted that the specification defines regulatory immune cells as follows:

> a regulatory immune cell is any mononuclear cell with a defined cytokine production profile and in which such cytokine profile does not directly mediate an effector function. A regulatory immune cell is a mononuclear cell that has the ability to control or direct an immune response, but does not act as an effector cell in the response. Regulatory immune cells exert their regulatory function by virtue of the cytokines they produce and can be classified by virtue of their cytokine production profile. For example, regulatory immune cells that produce IL-2 and IFN-γ, but do not produce IL-4 are termed "Th1" cells. Regulatory immune cells that produce IL-4 and IL-10, but do not produce IFN-γ are termed "Th2" cells. Regulatory immune cells that produce TGF-β, IL-10 and IFN-γ, but do not produce IL-2 or IL-4 are termed "Th3" cells. Cells that produce Th1, Th2 and Th3 cytokine profiles occur in CD4+ and CD8+ cell populations . . ..

Furthermore, these cells are contrasted in the specification to "effector cells, such as LAK, TIL and CTL cells" (see, e.g., page 20), which the specification defines (page 20, lines 23-26) as follows:

> As used herein, effector cells are mononuclear cells that have the ability to directly eliminate pathogens or tumor cells. Such cells include, but are not limited to, LAK cells, MAK cells and other mononuclear phagocytes, TILs, CTLs and antibody-producing B cells and other such cells..

The specification continues at page 24, line 27 et seq. as follows:

> Regulatory immune cells control the nature of an immune response to pathogens [see, Mosmann, et al. (1986) J. Immunol. 136:2348; Cherwinski, et al. (1987) J. Exp. Med. 166:1229; and Del Prete, et al. (1991) J. Clin. Invest. 88:346]. The different types of responses are attributable to the heterogeneity of $CD4^+$ T cells. $CD4^+$ cells can be subdivided according to their cytokine expression profiles. These cells are derived from a common precursor, Th0, which can produce Th1, Th2 and Th3 cytokines [see, Firestein, et al. (1989) J. Immunol. 143:518]. As noted above, Th1 clones produce IL-2, INF-γ, lymphotoxin and other factors responsible for promoting delayed-type hypersensitivity reactions characteristic of cell-mediated immunity. These cells do not express IL-4

> or IL-5. Th1 cells promote cell-mediated inflammatory reactions, support macrophage activation, immunoglobulin (Ig) isotype switching to IgG2a and activate cytotoxic function.
>
> Th2 clones produce cytokines, such as IL-4, Il-5, IL-6, IL-10 and IL-13, and thus direct humoral immune responses, and also promote allergic type responses. Th2 cells do not express IL-2 and IFN-γ. Th2 cells provide help for B-cell activation, for switching to the IgG1 and IgE isotypes and for antibody production [see, e.g., Mosmann et al. (1989) Annu. Rev. Immunol. 7:145]. Th3 cell produce IL-4, IL-10 and TGF-β.
>
> The cytokines produced by Th1 and Th2 cells are mutually inhibitory. Th1 cytokines inhibit the proliferation of Th2 cells and Th2 cytokines inhibit Th1 cytokine synthesis [see, e.g., Fiorentino, et al. (1989) Med. 170:2081 (1989). This cross regulation results in a polarized Th1 or Th2 immune response to pathogens that can result in host resistance or susceptibility to infection . . ..

Thus, the nature of regulatory immune cells as opposed to effector cells, which are cells that **directly eliminate pathogens or tumor cells** is clear from the specification.

Liblau et al. does not teach that Th1 or Th2 cells are "effector cells" as alleged by the Examiner. Liblau et al. refers to Th1 and Th2 cells as having **"effector function"**, this is distinct from the definition of effector and regulatory cells as defined in the instant application. Since these cells participate in the effector phase of an immune response they have effector function, but they do not directly cause the elimination of a target antigen, such as a true effector cell has

Furthermore, there is no teaching in Liblau et al. that pathogenicity in IDDM is caused by Th1 cells directly destroying islet cells such as is known to occur by immune effector cells. Rather, Liblau teaches that **Th1 cells mediate** (i.e. have a regulatory function) the pathogenesis of IDDM by the types of cytokines they produce. The ability of Th1 or Th2 cells to mediate disease is characterized by Liblau et al. as "effector function" (see page 34, first column,

second paragraph, line 8; page 37, legend to Figure 1, line 12), but it does not meant that the cells are effector cells.

There is a distinction in the art between "effector function" as used by Liblau et al. in which the cells participate in the effector phase of an immune response, and effector cells, such as, CTLs, B cells or phagocytic monocytes, which directly act to eliminate the target antigen. Regulatory immune cells participate indirectly in immune responses by elaboration of cytokines. Although Liblau et al. describes that "effector function" is associated with effector and regulatory immune cells, this does not mean that the skilled artisan would not understand the what is intended by regulatory cells and effector cells as intended in the instant application, which clearly defines and differentiates the two types.

Consistent with Liblau et al., the specification provides separate definitions for regulatory and effector immune cells at page 19 as:

> any mononuclear cell with a defined cytokine production profile and in which such cytokine profile **does not directly mediate an effector function**. A regulatory immune cell is a mononuclear cell that has the ability to control or direct an immune response, but does not act as an effector cell in the response. Regulatory immune cells exert their regulatory function by virtue of the cytokines they produce and can be classified by virtue of their cytokine production profile.

The above definition requires a regulatory immune cell to have a defined cytokine profile, where the cytokines do not directly mediate an effector function. The contemplation of a regulatory cell that indirectly mediates an effector function as defined in the specification is consistent with Liblau et al. which demonstrates "effector function" for regulatory T cells. The definition of a regulatory immune cell in the specification also expressly distinguishes it from an effector immune cell as defined on page 19 as:

> mononuclear cells that have the ability to directly eliminate pathogens or tumor cells. Such cells include, but are not limited to, LAK cells, MAK cells and other mononuclear phagocytes, TILs, CTLs and antibody-producing B cells and other such cells.

Thus, the specification, clearly distinguishes an immune regulatory cell from an immune effector cell. The definition in the specification of a regulatory immune cell encompasses Th1, Th2 and Th3 cells, and this is not inconsistent with the concept of "effector function" as described by Liblau et al.

2. Claims 1 and 22 are allegedly indefinite in the recitation of "clinically relevant" numbers of cells. It is stated that:

> the specification discloses that "clinically relevant" in the context of the claimed methods means methods for producing typically greater than 10^9 or 10^{10} cells, but does not specifically define what clinically relevant numbers of cells means in the context of the claimed method." For example it is unclear if a method that produced 10^8 cells would qualify as producing clinically relevant numbers of cells . . .

The rejection is respectfully traversed.

First, the rejection is unclear because it does not specify what it is about the definition that makes it vague and indefinite. The claims are directed to methods that produce clinically relevant numbers of T lymphoid cells or regulatory T lymphoid cells. As discussed above, the specification at page 20, line 1 defines a clinically relevant number of cells as:

> a composition that contains at least 10^9, preferably greater than 10^9, more preferably at least 10^{10} cells, and most preferably more than 10^{10} cells, in which the majority of the cells have a defined regulatory or effector function, such as Th1 cells or Th2 cells or effector cells, such as LAK, TIL and CTL cells.

By interpreting the claims in light of the specification, a clinically relevant number of cells without reference to a particular method is 10^9 cells or greater. When a particular method is referenced the number may vary. When used with reference to a method, the method is sufficiently effective to ameliorate, or in some manner reduce the symptoms associated with a disease:

> therapeutically effective refers to an amount of cells that is sufficient to ameliorate, or in some manner reduce the symptoms associated with a disease. (see page 21, lines 12-14)

Thus, the claim clearly sets forth the meaning of a clinically relevant number of cells.

3. Claim 23 is allegedly indefinite because "prior to infusion" lacks antecedent basis in claim 23 [claim 22]. In addition, it is also allegedly unclear what "prior to infusion" means. The rejection has been obviated by deletion of this phrase from the claim.

4. Claim 27 is allegedly indefinite for the recitation of Th1-like and Th2-like because it is unclear what these terms mean or encompass.

The rejection is respectfully traversed.

Relevant Law

When "one skilled in the art would understand all of the language in the claims when read in light of the specification," a claim is not indefinite. Rosemount Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), Caterpillar Tractor Co. v. Berco, S.P.A., 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). The claims are definite if they "make clear what subject matter they encompass and thus what the patent precludes others from doing". In re Spiller, 182 USPQ 614 (CCPA 1974). The requirements of § 112, second paragraph are met when one can "examine the claims to see whether the invention's metes and bounds can be adequately determined from the claim languages". In re Goffe, 188 USPQ 131 (CCPA 1975).

The specification defines Th-like cells on page 19, line 19 as:

> **Populations** of cells that produce a majority of Th1 cytokines are designated "Th1-like"; populations producing a majority of the Th2 cytokines are designated Th2-like"; those producing a majority of Th3 cytokines are designated "Th3-like". Thus, each composition, although containing a heterogeneous population of cells, will have the properties that are substantially similar, with respect to cytokine, to the particular Th subset.

Thus, Th-like cells represent mixed populations of Th cells where the cytokine profile lends itself to identification has predominantly Th1, Th2, or Th3, hence, the designation as Th1-like, Th2-like and Th3-like. In this regard, the specification also teaches the various lymphokine profiles associated with Th1,

Th2, and Th3 cells (see, e.g. page 25, lines 7-125). Thus, cells falling within the definition of Th1-like cells would produce a cytokine profile where IL-2 and IFN-γ were dominant. Also, cells falling within the definition of Th2-like cells would produce cytokine profile where IL-4, IL-10 and also IL-5, IL-6 and IL-13 were predominant.

Thus, it is respectfully submitted that the skilled artisan in view of the specification would have understood the metes and bounds of the terms "Th1-like" or Th2-like."

5. Claim 30 is allegedly indefinite because their is no antecedent basis for the recitation of "effector cells." The rejection is obviated by deletion of "effector" from the claim.

Right of Priority to U.S. Application No. 60/044693

The claim for priority to the provisional application 60/044693 (formally U.S. Serial No. 08/506,668) was denied by the Examiner for claims 1-3, 8-12, 14, 16, 17, or 22-35. Applicant respectfully disagrees with the Examiner's conclusion. These claims find basis in the provisional application, and are clearly entitled to the benefit of priority. The provisional application teaches and claims a method for producing clinically relevant numbers of expanded lymphoid cells.

The instant application has modified the nomenclature used in the provisional application by referring to the expanded cells as lymphoid or immune cells rather than effector immune cells. This represents a refinement and correction of the nomenclature, which the instant specification clearly defines. The instant application as did the provisional intended for the claims to encompass method of preparing expanded lymphoid cells, which in the present nomenclature include effector and regulatory cells. As noted above, the term regulatory cell is a recent addition to the nomenclature of immune cells.

Effector as used in the provisional application refers to any cells that participate in the effector phase of the immune response. These include regulatory and effector cells.

It is clear by reading the specification of the provisional application that the provisional specification contemplates expansion of mononuclear cells into regulatory, such as Th1 and Th2 and/or effector immune cells, such as LAK and TIL cells. The provisional application teaches (see, e.g., page 7, lines 7-25) a method in which mononuclear cells, are activated by contact with antibodies or antigens and then cultured with mitogenic antibodies and expanded under conditions that produce clinically effective concentrations. The activation methods and expansion methods exemplified and described in the provisional application are the same as those in the instant application.

For example, claim 15 of the provisional application is directed to a method comprising:

> withdrawing leukocytes containing material from a mammal;
> treating the cells to alter their cytokine production profile; and
> proliferating the cells to a sufficient number for infusion into the mammal adequate for use in adoptive immunotherapy.

The dependent claims recite the cells are treated to become specific for an antigen, or alter treated to differentiate in the Th1-like or Th2-like cells, clearly demonstrating that regulatory cells are contemplated.

Thus, Claim 15 and its dependents provide clear support for claims 1-3, 8-11, 14, 16, 22 and dependents thereon.

REJECTION OF CLAIMS 1, 3-7, 11, 12, 14-17, 22-25, 31, 32, 34 and 35 UNDER 35 U.S.C. § 102(b)

Claims 1, 3-7, 11, 12, 14-17, 22-25, 31, 32, 34 and 35 are rejected under 35 U.S.C. § 102(b) as being anticipated by June et al. (WO 94/29436). The Examiner states that:

June et al. teach the method of claim 1 wherein unfractionated T cells or CD4+ or CD8+ cells are expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28 or antiCTLA4 antibody (see abstract, pages 4-9, 13, claims 1-28, 30, 37). June et al. teach that prior to treatment said cells can be treated with antigen to induce ex vivo differentiation of said cells into antigen specific effector cells (see page 9, first complete paragraph) and that said cells can be purified (see page 29 and 300). June et al. teach a method that can be used to produce "regulatory cells" such as CD4+ cells (see page 6). Said CD4+ cells have a defined cytokine production profile, wherein said cytokine production profile does not directly mediate an effector function (e.g., said cells produce IL-4 which can cause Th2 differentiation). Said CD4+ cells are treated to alter their cytokine production profile prior to production in that they are separated from CD8 cells (see claim 30).

The rejection is respectfully traversed.

Claim 1 and dependents

Claim 1 is directed to a method for generating clinically relevant numbers of T lymphoid cells by contacting T lymphoid cells in the absence of IL-2 with two or more activating proteins specific for cell surface proteins present on the cells in an amount sufficient to induce ex vivo cell activation and cell proliferation. The claim further requires that the cells are expanded under conditions that produce high cell density exceeding 1×10^9 cells/liter to yield clinically relevant numbers. Claims 3-7, 11, 12 and 14-17, which are dependent from claim 1 are described briefly below.

Claim 3 requires that prior to expansion, the cells are treated under conditions whereby ex vivo differentiation of some or all of the cells into desired effector immune cells is induced. Claim 4 further specifies that the expanded cells are purified and claim 6 requires that the expanded cells are specific for a defined antigen.

Claim 5 requires that prior to expansion, the T lymphoid cells are treated under conditions whereby ex vivo differentiation of some or all of the cells into selected regulatory immune cells is induced and the cells are purified after expansion.

Claim 7 requires that prior to expansion, the cells are treated under conditions whereby ex vivo differentiation of some or all of the cells into selected regulatory immune cells is induced and the expanded regulatory cells are specific for a defined antigen.

Claim 11 requires that the proteins specific for cell surface proteins are one or more monoclonal antibodies specific for immune cell surface proteins. Claim 12 further recites that the monoclonal antibodies are specific for CD3 or CD2, combined with any combination of monoclonal antibodies specific for one or more of the following: CD4, CD8, CD11a, CD27, CD28, CD44 and CD45RO.

Claim 14 requires that the cells are expanded to an excess of 10^9 cells, while claim 15 requires expansion to an excess of 10^{10} cells.

Claim 16 specifies that the cells are effector cells, and claim 17 specifies that the cells are regulatory cells.

Claim 22 and dependents

Claim 22 is directed to a method for generating clinically relevant cell numbers of regulatory T lymphoid cells by activating mononuclear cells to alter their cytokine production profile and inducing cell proliferation. As in claim 1, the cells are expanded under conditions that produce high cell density to a clinically relevant number of cells. Claims 23-25, 31, 32, 34 and 35, which are dependent from claim 22 are discussed briefly below with respect to their distinguishing elements.

Claim 23 requires that the expanded cells are purified, while claim 24 requires that the expanded cells are specific for a defined antigen.

Claim 25 specifies that the T lymphoid cells with altered cytokine profile are specific for a defined antigen.

Claims 31 requires that the T lymphoid cells are expanded in the pres nce of two or more monoclonal antibodies, while claim 32 specifies that the monoclonal antibodies are specific for CD3 or CD2, combined with any combination of monoclonal antibodies specific for one or more of the following: CD4, CD8, CD11a, CD27, CD28, CD44 and CD45RO.

Claim 34 requires that the cells are expanded to an excess of 10^9 cells, while claim 35 requires expansion to an excess of 10^{10} cells.

Thus, all of the claims require that the T lymphoid cells are expanded to clinically relevant cell numbers and under conditions that produce high cell density.

Relevant Law

Rejection for anticipation requires, as a first step in the inquiry, that all the elements of the claimed invention be described in a single reference [see, e.g., In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S.. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226,1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989)].

Disclosure of June et al.

June et al. discloses a method for inducing a population of T cells to proliferate by providing a first signal to activate the cells and then a second signal to stimulate proliferation. Proliferation is sustained by periodic reactivation and restimulation. Cell densities substantially greater than 10^6 are not disclosed. Further, June et al. does not disclose or teach a method in which cells are differentiated into regulatory cells prior to expansion.

June et al. specifically discloses use of antibodies to CD3 or CD2 to activate the cells and antibodies to CD28 to stimulate cell proliferation. The method of inducing T cell proliferation can be performed without interleukin-2.

June et al. also discloses the use of the T cell proliferation method for obtaining a population of CD4+ or $CD8^+$ T cells and in the case of CD4+ cells, June et al. evaluates the cytokines produced by the cells at different stages of growth.

June et al. alleges that its method can be used to expand T cells in long term tissue culture to obtain a population increased in number **not in concentration** from about 100 to about 100,000 fold over the original starting cell population. Figures 1-3 purport to show that the method actually results in cell numbers could exceed 1×10^{10} cells, but do not teach or suggest preparation of such cells at a density of about 10^9/liter or more.

Also, June et al. does not disclose growth of a clinically relevant number of T cells. The results in Figures 1-3 are merely extrapolations of potential growth from a single flask. For example, page 27, line 8-9 of June et al. only mentions a single flask and the cells are "resuspended every day and diluted to 0.5×10^6 cells/ml." If the cells are stored at each resuspension, the resulting 10^{10} cells will be in a at density of about 0.5×10^6 cells/ml.

June et al. does not disclose growth of T cells to high cell density exceeding about 10^9 cells/Liter to obtain clinically relevant numbers of cells. The reference teaches growing the cells at a cell density maintained at 0.5×10^6/ml" (page 28, line 31). Thus, June et al. does teach every element of the instant claims, and, therefore, does not anticipate any of claims 1, 3-7, 11, 12, 14-17. Each of these claims require production of clinically relevant number of cells and expansion of the cells to produce cell densities of about 1×10^9 cells/Liter or higher. June et al. does not disclose expansion of T cells to clinically relevant numbers or expansion under conditions that produce high cell density. All of the claimed elements must be disclosed before a reference can be anticipatory.

Furthermore, Jun et al. does not anticipate claims 5, 7 and 16, for the additional reason that the reference does not disclose preparation of or expansion of regulatory immune cells. The Office Action alleges that:

> June et al. teach a method that can be used to produce "regulatory cells" such as CD4+ cells (see page 6). Said CD4+ cells have a defined cytokine production profile, wherein said cytokine production profile does not directly mediate an effector function (e.g., said cells produce IL-4 which can cause Th2 differentiation). Said CD4+ cells are treated to alter their cytokine production profile prior to production in that they are separated from CD8 cells (see claim 30).

Although the Examiner alleges that June et al. discloses expansion of regulatory immune cells, June et al. does not teach or suggest production of regulatory cells. It is respectfully submitted that there is no reference to "regulatory" cells at page 6 of June et al. as alleged or anywhere else in the reference. More importantly, however, June et al. does not disclose production of CD4+ regulatory cells. At most, June et al. discloses activation and growth of CD4+ cells using anti-CD3 + anti-CD28 and evaluates the cytokines produced during culture (see Table 2, page 32).

Stimulation of CD4+ cells with this combination of antibodies used by June et al. does not generally produce regulatory cells. Production of regulatory cells, requires differentiation. June et al. does not teach or suggest differentiation of cells. Furthermore, June et al. admits that the expanded CD4+ cells have unstable cytokine profile (see page 31, lines 26-29).

A regulatory cell as used in the claims has several requirements, which are set forth in the specification at page 19, lines 4-19, which defines a regulatory immune cells as:

> any mononuclear cell with a defined cytokine production profile and in which such cytokine profile does not directly mediate an effector function. A regulatory immune cell is a mononuclear cell that has the ability to control or direct an immune response, but does not act as an effector cell in the response. Regulatory immune cells exert their regulatory function by virtue of the cytokines they produce and can be classified by virtue of their cytokine production profile. For example, regulatory immune cells that produce IL-2 and IFN-γ, but do not produce

> IL-4 are termed "Th1" cells. Regulatory immune cells that produce IL-4 and IL-10, but do not produce IFN-γ are termed "Th2" cells. Regulatory immune cells that produce TGF-β, IL-10 and IFN-γ, but do not produce IL-2 or IL-4 are termed "Th3" cells. Cells that produce Th1, Th2 and Th3 cytokine profiles occur in CD4+ and CD8+ cell populations. Cells that produce IL-2, IL-4 and IFN-γ are thought to be precursors of Th1 and Th2 cells and are designated "Th0" cells.

Thus, the T cells activated by June et al., which are not caused to differentiate into regulatory cells, are characterized by an unstable profile of cytokines do not meet the definition of a regulatory T lymphoid cell as required by the claims. The cells of June et al. are probably CD4+ cells of precursor Th0 phenotype. Furthermore, there is no basis for the allegation that mere isolation of CD4+ cells as specified in claim 30 will result in alteration of their cytokine production profiles. June et al., therefore does not disclose or contemplate any method of producing regulatory cells.

Thus, June et al. does not anticipate any of the claims because it does not disclose expansion of T cells to clinically relevant numbers and under conditions that produce high cell density. Furthermore, June et al. does not anticipate claims 5, 7 and 16, or any of claims 155-194 for the additional reason that the reference does not disclose differentiation into regulatory cells or expansion of regulatory T lymphoid cells.

THE REJECTION OF CLAIMS 1-17, 22-32 AND 31-35 UNDER 35 U.S.C. § 103(a)

CLAIMS 1, 3-7, 11-17, 22-25, and 31-35

Claims 1, 3-7, 11-17, 22-25 and 31-35 are rejected under 35 U.S.C. § 103 as being unpatentable over June et al., in view of Cracauer et al. (US patent No. 4,804,628). It is alleged that:

> June et al. teach the method of claim 1 wherein unfractioned T cells or CD4+ or CD8+ cells are expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28 or antiCTLA4 antibody . . . June et al. teach a method that can be used to produce "regulatory cells" such as CD4+ cells (see page 6). Said CD4+ cells have a defined cytokine production profile, wherein said cytokine production profile does not directly mediate an effector function (e.g.,

said cells produce IL-4 which can cause Th2 differentiation). Said CD4+ cells are treated to alter their cytokine production profile prior to production in that they are separated from CD8 cells (see claim 30).

Cracauer et al. allegedly teaches hollow fiber bioreactors and the use of such devices for efficiently growing large numbers of cells in vitro. It is concluded that one of ordinary skill in the art would have been motivated to do the aforementioned because Cracauer et al. teach that "hollow fiber culture devices have been proven to be ideal for the maintenance of many types of cells at high densities in culture."

The rejection is respectfully traversed.

The Claims

Claims 1, 3-7, 11, 12, 14-17, 22-25, 31, 32, 34 and 24 are discussed above. Claims 13 and 33 are directed to the method of claim 1 and 22, respectively, wherein expansion is conducted in a hollow fiber bioreactor.

June et al.

June et al. teaches a method for inducing a population of T cells to proliferate by providing a first signal to activate the cells and then a second signal to stimulate proliferation. The reference teaches use of antibodies to CD3 or CD2 to activate the cells and antibodies to CD28 to stimulate cell proliferation. June et al. also teaches purifying populations of CD4+ or CD8+ T cells and growing the cells.

June et al. does not teach the step of expanding the cells to therapeutically useful or clinically relevant numbers, nor does June et al. teach or suggest a method in which cells are differentiated. June et al. states that T cells can be grown in long term tissue culture to obtain a population increased in number from about 100 to about 100,000 fold over the original starting cell population, but does not suggest preparation of clinically relevant numbers or therapeutically effective concentrations. June et al. also states that the method could be used to grow large numbers of T cells (e.g., more that 10^{10} cells), but does not teach or suggest means for achieving high cell densities.

June et al. does not actually demonstrate such allegations, the date in Figures 1-3 of June et al. are merely extrapolations of potential growth from a single flask. At page 27, line 8-9 of June et al. there is mention of a flask where the cells are "resuspended every day and diluted to 0.5 x 10^6 cells/ml." Thus, June et al. does not teach or suggest growth of T cells under conditions that produce high cell density to obtain clinically relevant numbers of cells.

June et al. also teaches the use of the T cell proliferation method for obtaining a population of CD4+ or $CD8^+$ T cells and, in the case of CD4+ cells, June et al. evaluates the cytokines produced by the cells at different stages of growth. This teaching, however, says nothing about the production of regulatory T lymphoid cells.

Although the Examiner alleges that June et al. teaches expansion of regulatory immune cells, it is respectfully submitted that June et al. does not teach, suggest or contemplate differentiation of cells into regulatory cells. As discussed above, there is no reference to "regulatory" cells at page 6 of June et al. as alleged or anywhere else in the reference. Stimulation of CD4+ cells with this combination of antibodies used by June et al. does not generally produce regulatory cells and June et al. admits that the expanded CD4+ cells have an unstable cytokine profile (see page 31, lines 26-29).

Cracauer et al.

Cracauer et al. teaches a hollow fiber cell culture device that includes a hollow fiber cartridge having a shell and a plurality of capillaries extending through the shell with at least some capillaries having semi-permeable walls. A cell culturing space is located between the shell and the capillaries. The device includes a chamber containing a second medium supply fluidly connected to the cell culturing space.

Cracauer et al. does not teach or suggest use of its hollow fiber cell culture for growing clinically relevant numbers of immune cells or T lymphoid cells, or for that matter any type of lymphoid cell. Cracauer et al. does not

teach or suggest anything about expanding regulatory T lymphoid cells or how to grow such cells under conditions that produce high cell density. In fact, the device of Cracauer et al. is not effective for producing the high densities of cells required by the claims. The device of Cracauer et al. is not taught to be suitable for growing lymphoid cells at densities exceeding 1×10^8 cells/ml (1×10^9 cells/Liter) because it is not designed to maintain a high concentration of lymphokines around the cells while retaining sufficient quantities of oxygen because oxygen diffusion is still limited, however, and gradients still occur.

The Examiner has failed to set forth a case of *prima facie* obviousness

(1) Relevant law

In order to set forth a prima facie case of obviousness under 35 U.S.C. § 103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (BPAI 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)).

(2) There would not have been motivation to have combined the teachings of June et al. with those of Cracauer et al.

June et al. does not contemplate preparation of high densities of cells, and thus, provides no motivation to have selected the device of Cracauer et al. Cracauer et al. provides no suggestion for growing T lymphoid cells in its

device. Therefore, the ordinarily skilled artisan would not have had any motivation to have added an additional step to the method of June et al. and have expanded the cells in the device of Cracauer et al.

(3) The combination of references does not result in the claimed subject matter

June et al. teaches a method of growing T lymphocytes, CD4+ and CD8+ T cells at relatively low cell densities of about 1 x 10^5 cells/ml- 0.5 x 10^6 cells/ml using a combination of mitogenic antibodies in the absence of IL-2. June et al., however, does not teach or suggest a method for obtaining clinically relevant numbers of T lymphoid cells nor expansion of such cells under conditions that produce high cell density, an element recited in all of the claims. Furthermore, with respect to claims 1, 3-7, 11, 12, and 14-17, June et al. does not teach or suggest growth to produce high cell density that exceed 1 x 10^9 cells/Liter.

With respect to claims 17, 22-25 and 31-35, all of which require expansion of regulatory T cells, June et al. also does not teach or suggest a method of producing regulatory T cells or a method whereby the regulatory T cells are expanded under conditions that produce high cell density to result in clinically relevant numbers of cells. At most, June et al. teaches activation and growth of CD4+ cells using anti-CD3 + anti-CD28 and evaluation of the cytokines produced. These cells do not have a stable cytokine profile (see page 31, lines 26-29). As discussed above, simple measurement of cytokine production does not meet the definition of a regulatory immune cell as used in the specification (page 19, lines 4-19).

Cracauer et al. does not cure the deficiencies in the teachings of June et al. because Cracauer et al. merely teaches a hollow fiber device, that does not provide adequate oxygenation. There is no teaching or suggestion in Cracauer et al. to use the device for expanding T cells at high cell density nor how to adapt the device to achieve such a goal. Further, Cracauer et al. does not teach or suggest a method for producing regulatory cells.

Therefore, the combination of references does not teach or suggest the instantly claimed methods.

Response to specific issues raised

The Office Action states that:

> June et al. teach the method of claim 1 wherein unfractioned T cells or CD4+ or CD8+ cells are expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28 or antiCTLA4 antibody . . . June et al. teach a method that can be used to produce "regulatory cells" such as CD4+ cells (see page 6). Said CD4+ cells have a defined cytokine production profile, wherein said cytokine production profile does not directly mediate an effector function (e.g., said cells produce IL-4 which can cause Th2 differentiation). Said CD4+ cells are treated to alter their cytokine production profile prior to production in that they are separated from CD8 cells (see claim 30).

As discussed above, June et al. makes no such claim to teaching expansion of regulatory T cells, June et al. teaches a two step method, but fails to teach or suggest the step of expanding the cells to high density and clinically relevant numbers.

Further, June et al. does not mention or suggest differentiation of cells to produce regulatory cells. At most, June et al. discloses activation and growth of CD4+ cells using anti-CD3 + anti-CD28 and evaluates the cytokines produced during culture (see Table 2, page 32). Stimulation of CD4+ cells with this combination of antibodies used by June et al. does not generally produce regulatory cells. The cells of June et al. are probably CD4+ cells of precursor Th0 phenotype. Furthermore, June et al. admits that the expanded CD4+ cells have an unstable cytokine profile (see page 31, lines 26-29).

Thus, the T cells activated by June et al. do not meet the requirements of a regulatory T lymphoid as claimed. In addition, there is no basis for the allegation that mere isolation of CD4+ cells as specified in claim 30 will result in alteration of their cytokine production profiles. June et al., therefore does not teach or suggest any method of producing regulatory cells.

It is respectfully submitted that for the above reasons, the art as a whole or the specific references do not provide sufficient reason or motivation to reach the claimed methods.

(3) The Rejection over June et al. in view of Cracauer et al. is Based on Improper Use of Hindsight.

The disclosure of the applicant cannot be used to hunt through the prior art for the claimed elements and then combine them as claimed. In re Laskowski, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

It appears that the Examiner has combined the teachings of the prior art with those of the instant application. Because the cited prior art fails to teach or suggest any of these essential requirements or provide any motivation to combine the references, nor the results of such combination, for the rejection to set forth a prima facie case of obviousness, it necessarily must have utilized the teachings of the specification to make the combination.

Neither June et al. nor Cracauer et al., singly or in combination, teaches or suggests growth of T lymphoid cells to clinically relevant numbers under conditions that produce high cell density. With respect to claims 1, 3-7, 11, 12, and 14-17, June et al. does not teach or suggest growth under conditions of high cell density that exceed 1×10^9 cells/Liter. Also, neither reference teaches anything about regulatory T cells. Accordingly, the obviousness rejection fails to set forth a prima facie case of obviousness and it improperly uses hindsight to combine the teachings of the prior art.

In view of the above arguments, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 1, 3-7, 11-17, 22-25, and 31-35 under 35 U.S.C. § 103(a).

Claims 1-12, 14-17, 22-32, 34 and 35

Claims 1-12, 14-17, 22-32, 34 and 35 are rejected under 35 U.S.C. § 103 as being unpatentable over June et al. in view of O'Garra et al. and the art disclosed in the specification on page 29 (Hsieh et al., Paliard et al., and Sedar et al.) because the claims are drawn to a method for generating Th1 or Th2 cells; June et al. alleged teaches:

> the method of claim 1 wherein unfractioned T cells or CD4+ or CD8+ cells are expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28 or antiCTLA4 antibody (see abstract, pages 4-9, 13, claims 1-28, 30, 37). June et al. teach that prior to treatment said cells can be treated with antigen to induce ex vivo differentiation of said cells into antigen specific effector cells (see page 9, first complete paragraph) and that said cells can be purified (see page 29 and 30) . . . June et al. teach that their method can be used to expand CD4+ T cells.

O'Garra et al. is alleged to teach a CD4+ Th1 and Th2 cells and that said cells produce particular types of lymphokines/cytokines. The specification allegedly discloses at page 16 that the art recognized that IL-4 treatment of T cells gives rise to Th2 cells and that the presence of interferon-gamma leads to formation of Th1 (see Hsieh et al., Paliard et al. and Seder et al.).

It is alleged that the ordinarily skilled artisan would have used Th1 or Th2 cells prepared by that method in the method taught by June et al., thereby rendering the claimed method obvious. It is also alleged that:

> One of ordinary skill in the art would have been motivated to do the aforementioned because June et al. teach that their method can be used to expand CD4+ cells and Th1 and Th2 cells are CD4+ cells. In addition, June et al. teach that their method can be used to expand T

cells as a source of T cell cytokines (see page 2, last sentence). O'Garra et al. teach that T cells produce different types of lymphokines/cytokines and therefore by producing Th1 or Th2 cells one could have produced a desired lymphokine or cytokine produced by said cell. A routineer would have use used anti-IL-4 or anti-gamma interferon antibody in said method to neutralize the unwanted potential cytokine that would interfere with the development of Th1 or Th2 depending on which T cell population was desired.

The rejection is respectfully traversed.

The Claims

Claims 1, 3-7 and 11-12 are discussed above. Claim 2 is directed to the method of claim 1 where, before the expansion step, the cells are treated with one or more activating proteins to induce differentiation into regulatory T cells.

Claim 8 requires that the expanded cells of claim 1 are Th1, Th2, or Th3 cells. Claims 9 and 10 relate to a method of producing clinically relevant numbers or Th1 or Th2 regulatory T cells and specify activating agents for effecting differentiation of mononuclear cells into regulatory T cells.

Claim 22-25, 31, 32, 34 and 35, discussed above, are directed to a method for generating clinically relevant cell numbers of regulatory T lymphoid cells by activating mononuclear cells to alter their cytokine production profile and inducing cell proliferation under conditions that produce high cell density. Claim 26 is directed to the method of claim 22 wherein the expanded cells are Th1 or Th2 cells. Claim 27 is directed to the method of claim 22 wherein the expanded cells are predominantly Th1 cells or predominantly Th2 cells. Claims 28-30 are directed to the method of claim 22 and specify different activating agents for effecting differentiation of mononuclear cells into regulatory T cells.

June et al.

The teachings of June et al. are discussed above. June et al. does not teach preparation of regulatory cells. At page 9, June et al. suggests that effector cells can be produced, but does not contemplate production of regulatory cells.

O'Garra et al.

O'Garra et al. teaches that early events in the immune response produce cytokines stimulate development of CD4+ T cells into Th1 or Th2 subsets characterized by discrete patterns of cytokine production. O'Garra et al. does not teach or suggest expansion of Th1 or Th2 cells to clinically relevant cell numbers.

Hsieh et al., Paliard et al., and Sedar et al.

As stated in the specification on page 29, each of Hsieh, et al. and Paliard et al. teaches that the presence of IL-4 during initial T-cell activation gives rise to Th2-like cells. Seder et al. teaches that activation of cells in the presence of IL-12 or interferon-γ leads to the formation of Th1-like cells. None of these references, however, teaches or suggests expanding Th1 or Th2 cells to clinically relevant numbers of cells to produce high cell density, but merely teach means for preparation of particular regulatory cells.

The Examiner has failed to set forth a case of *prima facie* obviousness

(1) Relevant law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. § 103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)); and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (BPAI 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v

Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)).

(2) There would have been no motivation to have combined the teachings of June et al. with the teachings of the secondary references

There would have been no motivation to have combined the teachings of references. June et al. is directed to a method for activating and proliferating undifferentiated cells or effector cells in the absence of IL-2. O'Garra et al. nor any of Hsieh et al., Paliard et al. or Sedar et al. teach methods for differentiating T cells into regulatory cells, but do not suggest or provide a motivation for producing large quantities of such cells. Since June et al. is directed to undifferentiated cells or effector cells, and the other references to are directed to producing differentiated regulatory cells, there would have been no motivation to have combined the teachings, nor any suggestion of what would have been the result of the combined teachings.

Furthermore, it is known in the art that the potential for cell growth generally slows as cells become more differentiated (see, e.g., Alberts et al. Molecular Biology of the Cell, 1169 Garland Publishing, N.Y. (3rd. ed. 1994) (Exhibit A). Thus, the ordinarily skilled artisan would not have been motivated to have combine the references because they could have believed that differentiation of T lymphoid cells into regulatory cells such as Th1 or Th2 cells, prior to expansion, might have precluded the potential to expand such cells to clinically relevant cell numbers. Furthermore, it was not known whether T lymphoid cells that are differentiated into regulatory T cells could have grown to clinically relevant numbers under conditions that produce high cell density.

There is no reason why the ordinarily skilled artisan would have been motivated to have differentiated cells into regulatory cells and then practiced the method of June et al.

Even if there were motivation to combine the teachings of the ref rences, although this is not admitted, there would have been no reasonable basis to

determine the outcome of the combination. June et al. does not teach or suggest preparation of clinically relevant numbers of cells; the cells are grown at low cell density so its only a guess that such a method would be successful when combined with more differentiated Th1 or Th2 cells, particularly in view of the generally knowledge in the art that more differentiated cells have reduced capacity for growth.

(3) The combination of references does not result in the claimed subject matter

June et al. teaches a method of growing T lymphocytes, CD4+ and CD8+ T cells at low cell densities of about 1 x 10^5 cells/ml using a combination of mitogenic antibodies in the absence of IL-2. June et al., however, does not teach or suggest a method for obtaining clinically relevant numbers of T lymphoid cells or expanding the cells under conditions that produce high cell density. None of the cited references teaches or suggests this element of the method. Thus, the combination cannot yield the instantly claimed methods.

More significantly with respect to the claims at issue, June et al. does not teach or suggest the step of differentiating the cells into regulatory cells before or even at any time during or after performing the described activating and proliferating steps.

Also, merely because Th1 and Th2 cells can be $CD4^+$ cells does not mean that June et al. suggests these species. A genus does not in general render a species obvious. June et al. provides no suggesttion to have prepared regulatory cells merely by describing cells that can be differentiated into regulatory cells.

Neither O'Garra et al. nor any of Hsieh et al., Paliard et al. or Sedar et al. cure this deficiency in the teachings of June et al. These references merely teach how to effect differentiation of CD4+ T cells to Th1 or Th2 subsets, but do not suggest that differentiated cells can be expanded into clinically relevant numbers and under conditions that produce high cell density nor methods for generating the cells that do not require IL-2.

R spons to sp cific issu s rais d

(1) June et al. does not teach regulatory cells

The Office Action states that:

> June et al. teach the method of claim 1 wherein unfractioned T cells or CD4+ or CD8+ cells are expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28 or antiCTLA4 antibody . . . June et al. teach a method that can be used to produce "regulatory cells" such as CD4+ cells (see page 6). Said CD4+ cells have a defined cytokine production profile, wherein said cytokine production profile does not directly mediate an effector function (e.g., said cells produce IL-4 which can cause Th2 differentiation). Said CD4+ cells are treated to alter their cytokine production profile prior to production in that they are separated from CD8 cells (see claim 30).

As discussed above, June et al. makes no such claim to teaching expansion of regulatory T cells and Applicant is unable to identify any reference to "regulatory" cells at page 6 of June et al. as alleged or anywhere else in the reference. More importantly, however, is that June et al. does not disclose production of CD4+ regulatory cells. At most, June et al. discloses activation and growth of CD4+ cells using anti-CD3 + anti-CD28 and evaluates the cytokines produced during culture (see Table 2, page 32). Stimulation of CD4+ cells with this combination of antibodies used by June et al. does not generally produce regulatory cells. The cells of June et al. are probably CD4+ cells of precursor Th0 phenotype. Furthermore, June et al. admits that the expanded CD4+ cells had unstable cytokine profile (see page 31, lines 26-29).

Thus, the T cells activated by June et al. do not meet the requirements of a regulatory T lymphoid as claimed. In addition, there is no basis for the allegation that mere isolation of CD4+ cells as specified in claim 30 will result in alteration of their cytokine production profiles. June et al., therefore does not teach or suggest any method of producing regulatory cells.

It is respectfully submitted that for the above reasons, the art as a whole or the specific references do not provide sufficient reason or motivation to reach the claimed methods.

(3) The R jecti n over June _t al. in vi w of O'Garra _t al. and the teachings of the specification at page 29 (Hsieh et al., Paliard et al. and Sedar et al.) is Based on Improper Use of Hindsight.

The disclosure of the applicant cannot be used to hunt through the prior art for the claimed elements and then combine them as claimed. In re Laskowski, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

It appears that the Examiner has combined the teachings of the prior art with those of the instant application. Because the cited prior art fails to teach or suggest any of these essential requirements or provide any motivation to combine the references, nor the results of such combination, for the rejection to set forth a prima facie case of obviousness, it necessarily must have utilized the teachings of the specification to make the combination.

Neither June et al. nor O'Garra et al., Hsieh et al., Paliard et al., or Sedar et al. teach or suggest growth of T lymphoid cells to clinically relevant numbers and under conditions that produce high cell density. June et al. does not contemplate regulatory T cells nor actually demonstrate expansion of T cells to clinically relevant cell numbers. None of O'Garra et al., Hsieh et al., Paliard et al., or Sedar et al. contemplate expansion of Th1 or Th2 cells to clinically relevant cell numbers under conditions that support high cell density. Accordingly, the obviousness rejection fails to set forth a prima facie case of obviousness and it improperly uses hindsight to combine the teachings of the prior art.

In view of the above arguments, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 1-12, 14-17, 22-32, 34 and 35 under 35 U.S.C. § 103(a).

* * *

In view of the above remarks and the amendments and remarks of record, consideration and allowance of the application are respectfully requested.

Respectfully submitted,
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